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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,544	ZENG ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/24/06, 4/28/06, 5/5/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/24/06 has been entered.

2. Applicants amendment filed 5/5/06 and the Declaration Pursuant to 37 CFR 1.132 of Dr. Samuel Strober filed 4/28/06 are acknowledged and have been entered.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 15-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendatory material not supported by the specification and claims as originally filed is "a CD1d blocking antibody." The originally filed disclosure is to "a CD1 blocking agent" that is a molecule that interferes with the binding of a CD1 isoform, such as CD1d, by the TCR, and said agent can be for example, an antibody, glycolipid, soluble TCR, or soluble CD1 ([0031]-[0040]).

5. Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention

of the claimed method wherein the second therapeutic agent is an immunomodulating drug as recited in the instant claim.

The instant claim encompasses a method of treating SLE in a human comprising administering an anti-CD1d antibody that blocks the interaction of CD1d with a TCR and further comprises any immunomodulating drug. Except wherein the said immunomodulating drug is either methotrexate or cyclosporine, there is insufficient disclosure in the specification on such an immunomodulating drug.

The specification discloses that agents such as methotrexate and cyclosporine are used to control the symptoms of lupus, and that both of these are immunomodulating drugs that have their own side effects ([0059]).

The specification does not disclose the definition of immunomodulating drug.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any drug that possesses any immunomodulating activity. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record).

Amano *et al* teach that the interaction between anti-CD1 T cells and B cells expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG. Amano *et al* further teach that transgenic T cells specific for CD1 (Vβ9/Vα4.4 T cell clone) induce lupus (SLE, an autoimmune disease) when transferred into nude host mice that do not spontaneously develop lupus, that these nude mice develop anti-ds DNA antibodies, proteinuria and ascites, and additionally, that the transgenic T cells could activate wild-type BALB/c B cells via the cross-linking of cell

surface CD1 to secrete both IgM and IgG *in vitro*. Amano *et al* teach that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11. Amano *et al* teach that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e.,* mice that spontaneously develop disease) is mediated by the $CD1^{hi}$ subset of B cells, "More recent studies have shown that the spontaneous secretion *in vitro* of both IgM and IgG by spleen cells from lupus-prone New Zealand Black/New Zealand White [i.e., NZB/NZW] mice is mediated by the CD1 high subset of B cells" (*i.e.,* that spontaneous antibody secretion in the same disease model used by Applicant is mediated by CD1 positive B cells) (especially second to last paragraph of article). Amano *et al* teach that CD1 by itself or in combination with endogenous antigens appears to be recognized by an autoreactive subset of T cells expresing the NK1.1 surface marker, and that this T cell subset has a restricted TCR repertoire that is made up predominantly of an invariant rearrangement of the vα14Jα281 associated with Vβ2, Vβ7 or Vβ8 receptors, but that Tcells that express neither the NK1.1 marker nor the Vα14 TCR are able to recognize CD1 on syngeneic antigen presenting cells (especially column 2 on page 1710 at the first paragraph). Amano *et al* teach that CD1d is expressed in both humans and mice (first paragraph).

Amano *et al* do not teach the claimed method of treating pathogenic polyclonal B cell activation or class switching, including that resulting in lupus (SLE), in a human patient, comprising administering a CD1 blocking agent that is an antibody, including a monoclonal antibody.

Kotzin teaches pathogenic IgG autoantibody production in SLE by clonal expansion of somatically mutated anti-DNA antibody-producing B cells (*i.e.,* pathogenic polyclonal B cell activation), a process that mimics a normal T cell dependent response to foreign antigen, involving common mechanisms of affinity maturation, and IgM to IgG class switching (especially first paragraph on page 304). Kotzin teaches that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE (especially last paragraph on page 303). Kotzin further teaches that T cells are clearly involved in the development of autoantibody production in SLE (especially column 1 on page 303 at the 2nd to the last sentence in column 1).

Zeng *et al* teach T cells with transgenic TCR that recognized CD1 of syngeneic B cells induced lupus with resulting anti-ds DNA autoantibodies, proteinuria and immune complex glomerulonephritis in nude mice that don't spontaneously develop lupus (especially abstract). Zeng *et al* teach anti-CD1 mAbs, including 3C11 (anti-CD1d) (especially materials and methods).

Zeng *et al* teach that severity of disease is associated with the development of the anti-ds DNA autoantibodies and with elevated serum IgG2a as has been observed with hereditary lupus (especially page 534 at the second full paragraph in column 1). Zeng *et al* teach that in hereditary murine lupus, administration of IL-10 worsens the disease and administration of anti-IL-10 antibodies ameliorates the disease likely through regulation of TNF-α secretion since endogenous TNF-α is increased in lupus after the

injection of the anti-IL-10 antibodies. Zeng *et al* teach that in hereditary murine lupus, administration of IFN-γ worsens lupus, and the injection of anti-IFN-γ antibodies ameliorates the disease, and that IFN-γ and IL-10 on one hand, and TNF- α on the other, play opposing roles in regulating the disease (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that both $CD4^+$ and $CD4^-CD8^-$ T cells from the spleen of mice with hereditary lupus have been reported to augment the secretion of anti-ds DNA antibodies *in vitro* (especially the last sentence of the paragraph spanning columns 1 and 2 on page 533).

Zeng *et al* teach that SLE inducing cells, *i.e.,* the single positive T cells, secreted large amounts of IFN-γ and little IL-4 (*i.e.,* have a Th1 phenotype), and the SLE preventive cells, i.e., the double negative cells, secreted large amounts of IL-4 (*i.e.,* have a Th2 phenotype) and little IFN- γ and little IL-10 (especially page 525 first column and abstract). Zeng *et al* further teach that introduction of an IL-4 transgene (encodes a Th2 cytokine) into NOD or NZW X C57BL/6 mice prevents SLE. Zeng et al teach "It is not surprising that T cells that secrete high levels of IFN- γ and IL-10 and low levels of IL-4 such as the transgenic anti-CD1 $CD4^+$ cells may induce or worsen lupus after activation of their CD1 receptors. One the other hand, the transgenic BM $CD4^-CD8^-$ T cells that secrete high levels of IL-4 and low levels of IFN- γ and no IL-10 would have been predicted to ameliorate disease based on their cytokine secretion pattern" (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* also teach "The cytokine secretion pattern of the T cells plays a critical role in regulating the B cell activation even when the TCR of the T cell subsets and the CD4 and CD8 receptor expression are identical". "...NZB/NZW F1 mice [the same model of spontaneous lupus disclosed by Appellants in the instant specification] lose a subset of T cells..that recognizes CD1 and secretes high levels of IL-4 just before lupus develops. Anti-Vα14 monoclonal antibodies injected into MRL/lpr mice exacerbates the development of lupus, and depletes this T cell subset...The latter subset shows two characteristics (recognition of CD1 and high level secretion of IL-4) with the CD4-CD8- T cell subset in the marrow that prevented lupus in this study (especially paragraph spanning columns 1 and 2 on page 534). Zeng *et al* teach that "the interaction between anti-CD1 T cells and B cell expressing surface CD1 leads to the activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity in vivo." Zeng *et al* teach that an alternative pathway of T cell induced polyclonal activation of B cells and/or help for the secretion of autoantibodies to nonprotein antigens such as nucleotides, *i.e.,* the anti-ds-DNA antibodies for example, in lupus is via T cell recognition of the CD1 molecule (especially page 532 at the first paragraph of the second column).

Blumberg *et al* teach that CD1c is expressed on human B cells in peripheral blood, spleen and tonsil, that CD1a, b and c are expressed on activated monocytes (GM-CSF+/- IL-4), CD1a is expressed on Langerhans cells, CD1a, b and c are expressed on dendritic cells in the dermis and CD1d is expressed in the GI tract on epithelial cells in mice and in humans as well as in other tissues at low levels (especially pages 14 and 15). Blumberg *et al* teach antibodies to the CD1 molecules, including 3C11 (anti-CD1d) and antibodies to CD1a, b and c. Blumberg *et al* further teach that 3C11 blocks the

interaction of T cells with CD1d (especially second paragraph on page 23). Blumberg et al teach that 3C11 cross-reacts with human CD1d (specially page 14 at the last paragraph).

Hughes teaches administration of monoclonal blocking antibodies (such as anti-TNFα), including humanized or human antibodies, to patients for a variety of conditions including autoimmune disease. Hughes teaches that the conventional route to derive monoclonal antibodies has been to immunize mice, that these antibodies have widespread applications in research but can trigger immune responses because of the foreign nature of the protein when introduced into humans. Hughes teaches use of humanized or human antibodies avoids such undesirable immune responses (especially page 439).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the anti-CD1d mAb taught by Zeng *et al* or Amano *et al* the anti-CD1d antibodies taught by Blumberg *et al* to block CD1 recognition by T cells as taught by Amano *et al* by administration of antibodies to human patients with SLE, and hence to treat pathogenic polyclonal B cell activation or class switching taught by Kotzin *et al*, including with humanized versions of the said antibodies as taught by Hughes for human patients with autoimmune diseases, and including by the intravenous (IV) route of administration as taught for administration of T cells by Zeng *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to treat pathogenic polyclonal B cell activation or class switching in a patient with SLE with a reasonable certainty of success because:

(1) Amano *et al* teach that interaction between anti-CD1 T cells and B cells that express cell surface CD1 leads to mutual activation of both cell types that results in systemic autoimmunity *in vivo* via cross-linking of CD1 to secrete IgM and IgG and that T cell proliferation of the CD1-restricted T cells in response to CD1-transfected B cells could be blocked by use of the anti-CD1d mAb 3C11, that transgenic anti-CD1 T cells can induce SLE with resulting anti-ds DNA antibodies, proteinuria and ascites when transferred into nude host mice that do not spontaneously develop the disease, and that the transgenic T cells could activate wild-type BALB/c B cells via the mechanism of cross-linking cell surface CD1 to secrete both IgM and IgG *in vitro*, and Amano *et al* correlate these teachings with the teaching that spontaneous secretion of IgM and IgG by splenic B cells from lupus-prone NZB/NZW mice (*i.e.*, mice that spontaneously develop disease) is mediated by the $CD1^{hi}$ subset of B cells;

(2) Kotzin *et al* teach that pathogenic IgG autoantibody production in SLE occurs by clonal expansion of somatically mutated anti-DNA antibody-producing B cells, *i.e.*, by pathogenic polyclonal B cell activation, said activation involving the mechanisms of affinity maturation and IgM to IgG class switching, that T cells are clearly involved in the development of autoantibody production in SLE, and that IgG autoantibodies to ds-DNA appear to play a prominent role in the immune complex glomerulonephritis in SLE;

(3) Zeng *et al* teach that T cells with transgenic TCR that recognize CD1 on syngeneic B cells could induce lupus in nude mice, said mice developing anti-ds-DNA autoantibodies, proteinuria and immune complex glomerluonephritis, that the severity of disease in this experimental system is associated with the anti-ds DNA autoantibodies and with elevated serum IgG2a as it is in mice with hereditary lupus, that T cells expressing the transgenic TCR specific for CD1 regardless of if they were double negative T cells or single positive T cells could induce disease or protect from disease depending upon their cytokine profile, *i.e.,* disease inducing cells secreted large amounts of IFN-γ and little IL-4 whereas disease protective cells secreted large amounts of IL-4 and little IFN-γ or IL-10, that the cytokine secretion patterns of T cells plays a critical role in regulating B cell activation, that these teachings correlate with hereditary murine lupus in that administration of IL-10 or IFN-γ worsens the disease, whereas administration of anti-IFN-γ or anti-IL-10 antibodies ameliorates the disease, that both single positive and double negative T cells from these mice have been reported to augment the secretion of anti-ds DNA autoantibodies *in vitro*, that introduction of IL-4 transgene into NOD or NZW X C57BL/6 mice prevents SLE, that administration of antiVα14 (*i.e.,* anti-TCR) mAbs to MRL/lpr mice exacerbates the development of lupus because it depletes a subset of T cells that recognize CD1 and secrete a high level of IL-4, that in NZB/NZW mice (*i.e.,* in the same model of spontaneous lupus disclosed by Appellants) said mice lose a subset of T cells with the same characteristics of recognizing CD1 and secreting high levels of IL-4 just before disease develops;

(4) Zeng *et al* , Amano *et al* and Blumberg *et al* teach anti-CD1 mAbs, Blumberg *et al* further teach CD1 expression on various tissues and cells in the body including B cells and antibodies to CD1, including rat anti-mouse CD1d mAb 3C11 that cross-reacts with human CD1d;

(5) Hughes teaches the administration of monoclonal blocking antibodies such as anti-TNFα to patients to treat a variety of conditions including autoimmune diseases and that it is advantageous when treating human patients to use humanized rodent antibodies to avoid undesirable immune reactions to the foreign nature of the rodent antibodies.

Claim 20 is included in this rejection because the intravenous (iv) route of administration was well known in the art at the time the invention was made and Zeng *et al* teach intravenous administration of T cells, so it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have injected the antibody/ies via the IV route of administration. The instant claims are included in the instant rejection because the CD1d antibodies taught by Zeng *et al* or Amano *et al* would be expected to bind to human CD1d since CD1d of mice or rat would be expected to cross-react with human CD1d due to the high degree of homology between mouse, rat and human CD1d and as taught by Blumberg *et al* for the rat anti-mouse 3C11 antibody that cross-reacts with human CD1d. Alternately, the value of monoclonal antibodies to proteins was well known in the art at the time the invention was made, in terms of specificity, purity and yield, and Blumberg *et al* teach the human CD1d protein. A routineer would have used the same basic technique for producing

monoclonal antagonist antibodies against human CD1d protein by using an appropriate *in vitro* assay where antagonistic antibodies could be detected.

The Declaration of Dr. Samuel Strober under 37 CFR 1.132 filed 4/28/06 is insufficient to overcome the rejection of the instant claims based upon the references of record in this rejection as set forth herein because:

It is the Examiner's position with regard to the following numbered paragraphs in the said Declaration that:

(4) and (5) The Wofsy and Seaman article (1985) teaches reduction of circulating CD4+ T cells in NZB/NZW mice using an anti-CD4 antibody reduced autoantibody concentration, retarded renal disease and prolonged life. The said article did not demonstrate which CD4+ T cells were responsible for autoantibody production, renal disease and mortality, nor that they recognized an autoantigen associated with SLE in context of MHC class II. The Swain articles cited by Applicant demonstrate that CD4+ T cells were known in the early 1980's to interact with MHC class II molecules; however, in 1998 Zeng *et al* recognized that a subset of CD4+ T cells were CD1 reactive and those cells secreted large amounts of IFN-γ and little IL-4 and induced lupus. The Zeng *et al* article (2003) cited by Applicant to demonstrate that non-CD1 reactive CD4+ T cells make up 95-96% of all CD4+ T cells in NZB/W mice and other well studied mouse strains and that CD1reactive CD4+ T cells account for 4-5% of all CD4+ T cells, along with Applicant's argument that transgenic mice used in the Zeng *et al* (1998) reference cited in the instant rejection had 100% of CD1 reactive CD4+ T cells, is not evidence that a smaller subset of CD4+ T cells could not be exerting the effect. 4-5% of cells in absolute numbers is 1 out of every 20 CD4+ T cells in the body (*i.e.,* a number of activated cells can mediate an amplified response through cytokine production) and Zeng *et al* correlate cytokine secretion pattern with a deleterious T cell subset;

(6) Amano *et al* as well as Zeng *et al* correlate their teachings using experimental models different from Applicant's with teachings that do use the same experimental model as Applicant's as well as with teachings relating to hereditary murine SLE and to other models of hereditary murine SLE, for example the MLR/lpr mouse model. Zeng *et al* teach that CD1 reactive T cells can provide help for the secretion of antibodies to non-protein antigens such as those found in SLE, whereas it is not established that conventional T cells can provide help for secretion of antibodies to non-protein antigens since the latter T cells recognize peptides in association with class II MHC molecules;

(7) Zeng *et al* teach correlation of deleterious versus protective T cell subsets with their cytokine secretion profile, *i.e.,* disease inducing cells secrete large amounts of IFN-γ and little IL-4 (Th1), whereas disease protective cells secrete large amounts of IL-4 and little IFN-γ or IL-10 (Th2), and correlate this teaching with hereditary murine models of lupus (for example, loss of a subset of CD1 reactive T cells that secrete large amounts of IL-4 in NZB/NZW and MRL/gld/gld mice just prior to SLE development, exacerbation of SLE after injection of anti-Vα14 into MRL/lpr mice to deplete this protective T cell subset, and presence of a protective subset of marrow cells in the TG mice that also

produce high level secretion of IL-4 and are CD1-reactive (*i.e.,* a teaching of Th1 or Th2 bias of CD1 reactive T cells). Likewise, in the instances of EAE and IDDM (the latter in NOD) mice treated with αGalCer to activate CD1 reactive Vα14+ T cells, induction of a Th2 cytokine pattern is protective and ameliorates disease. The NOD study by Lehuen *et al* (1998) cited by Applicant again correlates the presence of CD1 reactive IL-4 secreting Vα14+ T cells with protection from IDDM in NOD mice, and deletion of this subset with exacerbation of IDDM. This teaching of correlation of cytokine secretion pattern with T cell subset and protection or exacerbation of autoimmune disease is in contrast to Applicant's assertion that Lehuen *et al* teach against the pathogenic role of CD1 reactive T cells in autoimmune disease, and instead teach they are beneficial;

(8) Applicant's assertion that Singh *et al* reported that deficiency of NK T cells in NZB/W mice by targeted inactivation [of] the CD1 gene worsens lupus and therefore teaches against a pathogenic role of NK T cells in lupus in NZB/W mice is a mischaracterization. Singh *et al* teach that RF is increased in NZB/W mice. The presence of RF is not indicative of clinical disease since RF may be found in normal individuals. With regard to Applicant's arguments pertaining to Chan *et al* (2001), in β2m deficient MRL/lpr mice the reason for ameliorated renal disease is not known, one reason postulated is the short serum half life of IgG1 in β2m-/-/lpr mice. These mice would be expected to possess the β2m independent form of CD1 taught by Amano *et al.* In addition, the level of CD1 was reduced, not eliminated in the CD1 deficient mice. Chan *et al* teach that their β2m deficient mouse model is different from any other knockout lupus model. With regard to Applicant's arguments pertaining to Yang *et al* (2003, J. Immunol. 171: 2142-2153), Yang *et al* teach that exacerbation of disease activity is associated with reduced TNF-α and IL-4 production by T cells, especially during the disease induction phase, and expansion of marginal zone B cells, *i.e.,* the same correlation taught in the instant rejection of exacerbation with decreased TNF-α and IL-4 production and marginal zone B cells that express $CD1^{hi}$/CD21 and produce autoantibodies (Amano *et al*), in contrast to Applicant's assertion that Yang *et al* teach that CD1d deficiency exacerbates lupus. The 2003 Yang *et al* J. Immunol. 171: 4439-4446, 2003 reference was not provided by Applicant, and is hereby provided on Form 892 by the Examiner. Applicant asserts that the said reference teaches expansion of CD1 reactive T cells using αGalCer improves dermatitis in MRL-lpr/lpr mice. However, said reference teaches that αGalCer treatment results in significant expansion of NKT cells that preferentially secrete Th2 cytokines, *i.e.,* a teaching that is consistent with that of the instant rejection, namely a correlation of amelioration of disease with Th2 cytokine secreting cells;

(9) One of ordinary skill in the art would have a reasonable expectation of success in producing the claimed method for the reasons enunciated above;

(10) the Zeng *et al* and Amano *et al* references are being argued separately. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

8. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Amano *et al* (J. Immunol. 1998, 161: 1710-1717, IDS reference) in view of Kotzin (Cell, 1996, 85: 303-306, IDS reference), Zeng *et al* (J. Exp. Med. 1998, 187: 525-536, IDS reference), Blumberg *et al* (Immunol. Rev. 1995, 147: 5-29, of record) and Hughes (Drug Disc. Today 3(10): 439-442, 1998, of record) as applied to claims 1, 2, 6, 7, 8, 10 and 12 above, and further in view of the Merck Manual (pages 1317-1321, 16th Edition, 1992, of record).

The combination of Amano *et al* ,Kotzin, Zeng *et al* , Blumberg *et al* and Hughes has been discussed supra, "the combined references".

The "combined references" do not teach the claimed method of treatment of SLE that further comprises administration of a second therapeutic agent for the treatment of SLE, including wherein the second therapeutic agent is an anti-inflammatory drug.

The Merck Manual teaches treatment of SLE with corticosteroid treatment (a class of anti-inflammatory drugs), such as with prednisone, in combination with immunosuppressive agents. The Merck Manual teaches that severe disease with renal damage requires immediate corticosteroid therapy in combination with immunosuppressives, and that in both mild and severe disease, after the inflammatory response is controlled, the minimal dose of corticosteroids and other agents necessary to suppress tissue inflammation must be determined and administered, and that anticoagulant therapy is vital in patients with antiphospholipid antibodies and recurrent thrombosis (especially first three full paragraphs on page 1320, last said full paragraph continuing on to page 1321).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered along with the immunosuppressive agent that is the antibody to CD1 that blocks binding of the TCR to CD1 taught by the "combined references," an anti-inflammatory corticosteroid such as prednisone and/or the anti-coagulant taught by the Merck Manual for treatment of SLE.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to more effectively treat SLE by suppressing the immune system by blocking CD1-mediated pathogenic polyclonal B cell activation or class switching as taught by the "combined references" and to control the inflammatory response using corticosteroid(s) in combination with immunosuppressive agents as taught by the Merck Manual, and to treat with anti-coagulant agents in patients with antiphospholipid antibodies and recurrent thrombosis as is taught by the Merck Manual as being vital for those patients. In addition, motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Section MPEP 2144.07.

The Declaration of Dr. Samuel Strober under 37 CFR 1.132 filed 4/28/06 is insufficient to overcome the rejection of the instant claims based upon the references of record in this rejection for the reasons of record in the rejection over Amano *et al*, Kotzin, Zeng *et al*, Blumberg *et al* and Hughes enunciated supra. The Examiner's arguments thereto apply herein.

9. No claim is allowed.

10. The reference crossed out in Applicant's Form 1449 filed 4/28/06 is a duplicate entry of a reference considered by the Examiner in Applicant's Form 1449 filed 2/12/03.

11. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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